REMARKS

The present invention relates to a method of treatment or prophylaxis of inflammatory bowel disease (IBD) comprising administration of a therapeutically effective amount of an inhibitor of CSF-1 activity, wherein the inhibitor is an anti-CSF-1 antibody or CSF-1 binding fragment of an anti-CSF-1 antibody. Claim 12 is amended herein to incorporate the limitations of claim 15, and claim 15 is accordingly cancelled. Claims 16-19 are amended to correct the dependencies thereof from claim 15 to claim 12.

The withdrawal of the previous rejection under 35 USC 112, second paragraph, is noted with appreciation.

Rejections Under 35 USC §102

1. The Bedian et al. reference

Applicants acknowledge the defects in the previously filed Declaration, namely, the omission of inventor Diane Marshall's city and country of residence, country of citizenship, and mailing address with postal code. Submitted herewith is a supplemental application data sheet that includes this information. It is respectfully submitted that this is sufficient to overcome the deficiencies in the petition to correct inventorship, and the oath.

The Examiner noted that the Declaration previously submitted would be sufficient to overcome the rejection as it applies to claims 15-17 and 19, but not as to claims 12 and 21-22. As the limitations of claim 15 have now been incorporated into claim 12, it is respectfully submitted that the previously submitted declaration is sufficient to overcome the rejection over the Bedian et al. reference with respect to amended claim 12, claims 21-22 that now depend from claim 12, and claims 16-17 and 19 which also depend from claim 12.

2. U.S. 7,108,852

The rejection of the pending claims as anticipated by Devalaraja et al. (US 7,108,852) under 35 U.S.C 102(e) is respectfully traversed. Devalaraja et al. is directed

to the general proposition that agents that inhibit or otherwise hinder the production, release or activity of any of three types of colony stimulating factors (CSFs) can be used therapeutically in the treatment of ischemia and other inflammatory diseases, such as autoimmune disease, and various chronic inflammatory diseases such as rheumatoid arthritis and psoriasis (Abstract). The reference recognizes three types of CSFs: G-CSF, M-CSF, and GM-CSF (col. 1, lines 17-32). The reference also recognizes two classes of chemokines as other cytokines that are involved in inflammation (col. 1, line 64- col. 2, line 11). Il-8 is noted as a chemokine that mediates inflammatory response (col. 2, lines 32-59). Disorders that are said to be treatable by the method of Devalaraja et al. include osteoporosis, atherosclerosis, chemokine-mediated inflammation, and autoimmune diseases (cols. 6-8). The Devalaraja et al. method is said to be able to treat, without limitation, atherosclerosis, osteoporosis, and chronic and acute inflammatory and autoimmune diseases such as SLE, GVHD, RA, IBD, asthma, and psoriasis (col. 7, lines 4-8).

Examples 1 and 2 and Figs. 1-13 relate to G-CSF. Examples 3 and 4 and Figs. 14-21 relate to M-CSF. These examples are said to demonstrate M-CSF synergized MCP-1-induced chemotaxis (col. 19, lines 18-19). In particular, the data are said to show that MCP-1 directly acts on monocytes in human whole blood in a time- and concentration-dependent manner; that M-CSF alone much more potently induces changes in the shape of monocytes as compared to its effect in the shape of neutrophils; and that M-CSF synergistically increases the potency of MCP-1 induced effects on monocytes. (col. 19, line 63 – col. 20, line 5). From these findings, the reference concludes that "inhibitors of the synergistic effect of M-CSF on a chemokine such as, for example, MCP-1, involved in monocyte-mediated inflammation, osteoporosis, an autoimmune disease, or artherosclerosis would be valuable therapeutic agents for the treatment thereof." Yet none of the examples relate to animal testing or models of any of the diseases purported to be treatable by the claimed method. The claims are directed to a method of treatment for rheumatoid arthritis.

At best, Devalaraja et al. engages in mere speculation as to the effect of such inhibitors in the treatment of particular diseases. Animal models of IBD were available at the time, yet Devalaraja et al. did not report any animal studies, on IBD or any other

disorders. Thus, Devlaraja et al. failed to demonstrate that M-CSF actually has a role in IBD. The disclosure of Devalaraja et al. fails to teach the claimed invention, i.e., the use of a particular CSF inhibitor, anti-CSF-1 antibodies or CSF-1 binding fragments thereof, to treat a particular autoimmune disease, namely, IBD. Thus, while IBD is included in a list of many possible examples of autoimmune diseases (col. 7, lines 4-8), there is no teaching or suggestion that antibody inhibitors of M-CSF, as opposed to inhibitors of G-CSF or GM-CSF, are particularly useful in the treatment of IBD, among the other diseases alleged to be treatable, nor is there any indication that antibodies of M-CSF are particularly useful in the treatment of IBD, among all the autoimmune diseases listed. There is simply a disclosure of different inhibitors of different CSF's, methods of screening for them (col. 7, line 9 – col. 8, line 17; Examples 1-4), and related compositions. The disclosure reports that "Several experiments were conducted that demonstrate that M-CSF synergized MCP-1 induced chemotaxis." (col. 19, lines 18-19). None of the data, however, relate to the use of anti-M-CSF antibodies or fragments to treat IBD.

The present application, having claims to the use of a particular inhibitor in a method of treating a particular disorder, is analogous to the patent that was at issue in the case of *Impax Laboratories, Inc. v. Aventis Pharmaceuticals, Inc.*, 545 F.3d 1312, 88 USPQ2d 1381 (Fed. Cir. 2008). In that case, the claims at issue related to a method of treating ALS comprising the step of administering a certain compound. One prior art reference disclosed the claimed compound as one among many, disclosed ALS as one of several different disorders that could be treated by administration of the disclosed compounds, and contained no working examples relating to ALS. In upholding the validity of the patent over that art, the Federal Circuit in *Impax* stated,

> "In order to anticipate a claimed invention, a prior art reference must enable one of ordinary skill in the art to make the invention without undue experimentation. *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1336, 86 USPQ2d 1609, (Fed. Cir. 2008) (citing *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1379, 82 USPQ2d 1643 (Fed. Cir. 2007)). In other words, the prior art must enable the claimed invention. *Minn. Mining & Mfg. Co. v. Chemque, Inc. (3M)*, 303 F.3d 1294, 1301, 64 USPQ2d 1270 (Fed. Cir. 2002). The 'undue experimentation' component of that equation examines (1) the quantity of experimentation; (2) the amount of direction or guidance present; (3) the presence or absence of working

> examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988)." 88 USPQ2d at 1383.

The district court had found that the prior art reference was not enabling as to the claimed invention under the *Wands* factors. This finding was upheld by the Federal Circuit. The court noted, *inter alia*, that ALS was one of many diseases listed in the prior art reference, and that the prior art reference included neither dosage guidelines nor working examples showing treatment of ALS, such that one skilled in the art would not know from the reference how to treat a person with ALS without undue experimentation. 88 USPQ2d at 1384.

In this case, the Devalaraja et al. reference likewise fails the test of enablement under the *Wands* factors. There is no guidance in the reference suggesting that inhibitors of M-CSF, as opposed to other cytokines or chemokines, would have any particular therapeutic value in the treatment of IBD, as opposed to any of the other autoimmune disease or other disorders mentioned in the reference. The reference gives no working examples relating to actual models of any diseases, no models of autoimmune diseases, and no models of IBD. The pharmaceutical and biological arts are by nature unpredictable. And the claims herein have been narrowed by amendment to a method for the treatment of inflammatory bowel disease (IBD) comprising administering a therapeutically effective amount of an inhibitor of CSF-1 activity to a patient in need thereof, said inhibitor being selected from one or more of an anti-CSF-1 antibody and a CSF-1-binding fragment of an anti-CSF-1 antibody. Under the standard of *Wands*, the Devalaraja et al. reference does not enable the claims as presented herein.

The present application includes *in vivo* data at Example 2 specifically demonstrating the effect of anti-CSF-1 antibody on the symptoms of DSS Induced Acute Colitis. Thus, the disclosure of the present application does enable the claimed invention, in an important way that the reference does not. Accordingly, it is respectfully submitted that the claims as amended herein are not anticipated by the reference, and it is requested that this ground of rejection be withdrawn.

3. U.S. 7,455,836

The rejection of the pending claims as anticipated by Hamilton et al. (US 7,455,836) under 35 U.S.C 102(e) is respectfully traversed. Like the Devalaraja et al. reference discussed above, Hamilton et al. generally suggests the use of inhibitors of CSFs in the amelioration of inflammation in a subject (col. 2, lines 3-9). Targets of the inhibitors can include GM-CSF, M-CSF, and u-PA. Unlike Devalaraja et al., Hamilton et al. does describe animal studies at Example 5; the diseases modeled in these studies are asthma, COPD (chronic obstructive pulmonary disease), and exacerbation of asthma (col. 14, line 35 – col. 15, line 15). The only data relating to M-CSF is in Fig. 2C, and that data relates to CIA (collagen-induced arthritis).

The Hamilton et al. reference fails to meet the *Wands* standard of enablement with respect to the invention as presently recited in claim 12. There is no guidance in the reference suggesting that inhibitors of M-CSF, as opposed to GM-CSF or u-PA, would have any particular therapeutic value in the treatment of IBD, as opposed to any of the other autoimmune disease or other disorders mentioned in the reference. The reference provides working examples relating to arthritis and lung diseases, but no data related to any form of IBD, no models of other autoimmune diseases, and no models of IBD. The pharmaceutical and biological arts are by nature unpredictable. And the claims herein have been amended to be narrowed to method for the treatment of inflammatory bowel disease (IBD) comprising administering a therapeutically effective amount of an inhibitor of CSF-1 activity to a patient in need thereof, said inhibitor being selected from one or more of an anti-CSF-1 antibody and a CSF-1-binding fragment of an anti-CSF-1 antibody. Under the standard of *Wands*, the Hamilton et al. reference does not enable the claims as presented herein.

Rejection Under 35 USC §103

The rejection of the claims as obvious under 35 USC 103 over Devalarja et al. and/or Hamilton et al. in view of Buschmann et al. (U.S. 7,507,705), Renner et al. (U.S.

2004/0053365), and as evidenced by page 1 paragraph 3 of the instant specification, is respectfully traversed.

The deficiencies of the Devalaraja et al. and Hamilton et al. references have been discussed above. Buschmann et al. relates to a method of enhancing neovascularization and/or growth of collateral arteries from preexisting arteriolar connections (col. 2, lines 27-30). Data is presented only for animals treated with either GM-CSF or PBS. Buschmann teaches nothing about IBD, and present s no data relating to inhibitors of M-CSF. Renner et al. relates to humanized GM-CSF antibodies and expression vectors. This reference teaches nothing about M-CSF inhibitors or antibodies or fragments thereof which are M-CSF inhibitors, and teaches nothing about IBD.

At the time of the applicants' invention, those skilled in the art of inflammatory diseases understood that the underlying disease mechanism for IBD is complex, and is different from other inflammatory diseases, such as rheumatoid arthritis or osteoporosis. Many different factors had already been implicated in IBD, and many of these were believed to have stronger links to IBD than M-CSF. See, Sandborn et al., *Gastroenterology,* 2002;122:1592-1608, previously of record in this application; and Baumgart et al., *Current Pharmaceutical Design*, 2004, *10*, 4127-4147 and Panés, Acta Physiol. Scand. 2001, 173, 159-165, each identified in the Supplemental Information Disclosure Statement submitted herewith. See Figure 2 and Table 2 of Sandborn which illustrate the complexity of the potential involvement of numerous cytokines in IBD. Notably, Sandborn and Panés do not even mention M-CSF. This reference therefore also fails to provide any motivation to one skilled in the art to treat IBD using an inhibitor of M-CSF. In fact, at the time of the applicants' invention there was no known direct link between IBD and M-CSF, and none of the cited references provides any evidence that M-CSF plays a role in the pathogenesis of the disease. The cited references merely list IBD among several other disorders that might possibly be affected. There is no reason why one skilled in the art would have selected IBD from these lists of disorders. Accordingly, at the time of the present invention, the selection of M-CSF as the target would not have been obvious to one of ordinary skill in the art.

None of the cited references provides any animal data relating to IBD. There is no reason why one skilled in the art would have had a reasonable expectation that such

experiments would have been successful. The results of the animal model data as reported in the present application were not predictable. The prior art references disclosing animal data for disorders such as asthma or arthritis teach nothing about IBD. The fact that a drug or therapy may be useful for one type of inflammatory disease does not mean that it is effective against all types of inflammatory diseases; if that were so, there would be no reason to conduct different experiments to understand the causes of such different inflammatory diseases or to run animal models. Otherwise, one drug would be suitable for the treatment of arthritis, asthma, and IBD, yet we know that this is not so.

It is respectfully submitted that the Examiner is employing impermissible hindsight, using the applicant' own invention as a template according to which the various elements of the invention are found in the prior art. The applicants herein have reduced the invention to practice by positively demonstrating the activity of anti-CSF-1 antibodies in the pathogenesis of IBD, a connection which none of the prior art references had demonstrated. Accordingly, it is respectfully submitted that the claims as amended herein are not obvious over the prior art of record, and it is respectfully requested that this ground of rejection be withdrawn.

CONCLUSION

As all grounds of rejection have been overcome, a Notice of Allowance is requested. The Applicants invite the Examiner to contact the Applicants' undersigned representative at (312) 913-3362 if the Examiner believes that this would expedite prosecution of this application.

Respectfully submitted,

Date: June 21, 2010

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